Drinking Water and Cancer

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Any and all chemicals generated by human activity can and will find their way into water supplies. The types and quantities of carcinogens present in drinking water at the point of consumption will differ depending on whether they result from contamination of the source water, arise as a consequence of treatment processes, or enter as the water is conveyed to the user. Source-water contaminants of concern include arsenic, asbestos, radon, agricultural chemicals, and hazardous waste. Of these, the strongest evidence for a cancer risk involves arsenic, which is linked to cancers of the liver, lung, bladder, and kidney. The use of chlorine for water treatment to reduce the risk of infectious disease may account for a substantial portion of the cancer risk associated with drinking water. The by-products of chlorination are associated with increased risk of bladder and rectal cancer, possibly accounting for 5000 cases of bladder cancer and 8000 cases of rectal cancer per year in the United States. Fluoridation of water has received great scrutiny but appears to pose little or no cancer risk. Further research is needed to identify and quantify risks posed by contaminants from drinking-water distribution pipes, linings, joints, and fixtures and by biologically active micropollutants, such as microbial agents. We need more cost-effective methods for monitoring drinking-water quality and further research on interventions to minimize cancer risks from drinking water. — Environ Health Perspect 103(Suppl 8):225–232 (1995)

Key words: arsenic, asbestos, bladder cancer, cancer, chlorination, environment, fluoridation, rectal cancer, water

Introduction

Few things tie humans so directly to the natural environment as drinking water. The contamination of water is a direct reflection of the degree of contamination of the environment. After flushing airborne pollutants from the skies, rainwater literally washes over the entire human landscape before running into the aquifers, streams, rivers, and lakes that supply our drinking-water. Any and all of the chemicals generated by human activity can and will find their way into water supplies. Evaluating possible links between drinking water and cancer means identifying those chemicals that appear in enough water supplies at sufficient concentrations to pose a substantial attributable cancer risk.

Contaminants may enter water supplies at many points before reaching the tap. The types and quantities of carcinogens present in drinking water at the point of consumption may result from contamination of the source water, arise as a consequence of treatment processes, or enter as the water is conveyed to the user. Many different carcinogens may contaminate source waters, but they usually exist in drinking water at low concentrations. On the other hand, chemicals that enter drinking water during the course of water treatment are limited in number, but these chemicals appear in drinking-water supplies with greater frequency than most source water contaminants. Finally, the compounds contained in the pipes, joints, and fixtures of the water distribution system may contaminate treated water on its way to the consumer. Similarities in the construction of drinking-water distribution systems mean that any carcinogen entering through this pathway may be widespread and can pose substantial attributable risks of cancer. The following discussion reviews the attributable risks for contaminants entering at each of these points. Data gaps are identified and emerging areas of concern are discussed.

This paper was presented at the President's Cancer Panel Conference on Avoidable Causes of Cancer held 7–8 April 1994 in Bethesda, Maryland. Manuscript received 9 March 1995; manuscript accepted 24 March 1995.

The author gratefully acknowledges R. Munasinghe for his assistance in preparation of the maps included in this paper.

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Abbreviations: IARC, International Agency for Research on Cancer; DDT, dichlorodiphenyltrichloroethane.

Source-Water Contaminants

Except for naturally occurring minerals such as calcium carbonate, contaminants that enter the water supply through the source water generally occur at low concentration levels. Source-water contaminants of concern either are sufficiently potent carcinogens to pose risks at extremely low concentrations or cause local contamination at high concentrations. The source-water contaminants that have been the focus of concern among those individuals investigating environmental cancer risks include arsenic, asbestos, radon, agricultural chemicals, and hazardous waste.

Some of the strongest evidence for a cancer risk associated with source-water contamination involves arsenic. Epidemiologic studies from Taiwan have suggested that arsenic in drinking water poses substantial risks of liver, lung, bladder, and kidney cancer as listed in Table 1 (*1,2*). Although toxicologic studies do not provide unequivocal evidence of carcinogenicity (*3*), occupational studies, as well as other epidemiologic studies, support the findings of the Taiwanese studies(*4*). Estimates of attributable risk based on the data in Table 1 suggest that an average level of arsenic 2.5 µg/l in drinking water in the United States of causes approximately 3000 cases of cancer per year (*4*).

Although asbestos is a proven carcinogen, the attributable risks associated with asbestos in drinking water do not appear to be substantial. An early study in California (*5*) suggested that there may be an

Table 1. Estimated mortality risk ratios by arsenic levels in drinking water in Taiwan.

Cancer site	Sex	Background	Water levels, µg/l 170	470	800	*p*-Value for trend
Liver	M	1.0	1.2	1.5	2.5	<0.001
	F	1.0	1.6	2.1	3.6	<0.001
Lung	M	1.0	1.8	3.3	4.5	<0.001
	F	1.0	2.8	4.3	8.8	<0.001
Bladder	M	1.0	5.1	12.1	28.7	<0.001
	F	1.0	11.9	25.1	65.4	<0.001
Kidney	M	1.0	4.9	11.9	19.6	<0.001
	F	1.0	4.0	13.9	37.0	<0.001

Data from Chen et al. (*1*).

elevation in colorectal cancer risk associated with asbestos in drinking water. It appears that these findings are limited to situations in which naturally occurring levels are high. A subsequent, more detailed study of asbestos in source water, together with studies of asbestos leached from water distribution systems, suggests that, when asbestos is present at levels commonly found in drinking water, it does not pose a major cancer risk (*6,7*).

Radon is also a known carcinogen; however, the evidence linking consumption of radon-contaminated water to human cancer is weak (*8*). The relationship between ionizing radiation and cancer is well understood. This information, coupled with measured levels of radon in drinking water, suggests that fewer than 100 cases of cancer occur each year in the United States as a consequence of consuming radon in drinking water (*9*).

Farm runoff containing agricultural chemicals and manure may lead to local or regional contamination of source waters with insecticides, fungicide, rodenticides, herbicides, and fertilizers, which contain phosphorous and nitrogen. Although some pesticides are carcinogens, drinking-water contamination resulting from their agricultural application has not been directly associated with cancer in epidemiologic studies. Emerging evidence, however, indicates that fertilizers may pose cancer risks.

Studies in China among populations exposed to high levels of nitrates in drinking water have suggested links between nitrate contamination and stomach and liver cancer (*10*). In these studies, the histology of the gastric lesions has been linked to the level of nitrates in the water (*11*) and cancer rates increased with the *in vitro* mutagenicity of the drinking water (*12*). Nitrates may act as carcinogens through the formation of *N*-nitroso compounds (*13*). When human volunteers were given proline, which is a secondary amine, those participants in areas with higher levels of nitrate in their drinking water had higher levels of *N*-nitrosoproline in their urine than volunteers residing in places with low nitrate levels in their drinking water (*14*). Although an epidemiological study in France failed to demonstrate an association between nitrates in drinking water and cancer (*15*), current evidence is sufficient to warrant further study of this potential carcinogen.

Few examples of significant links between hazardous waste in drinking water and cancer have been reported. Elevated cancer risks are difficult to detect because of the relatively low incidence of site-specific neoplasms and the typically small size of exposed populations (*16*). An ecologic study in New Jersey found weak evidence for a positive association between volatile organic compounds in drinking water and leukemia (*17*). In a national ecologic study, Griffith et al. (*18*) found evidence of elevated cancer rates in the vicinity of hazardous waste sites. Limitations on ecologic data urge caution in the interpretation of such findings. Contamination of wells associated with hazardous waste disposal in Woburn, Massachusetts, was ultimately linked to elevations in their incidence of leukemia (*19*). Although this investigation was arguably the most thorough study of this kind, questions were raised about the magnitude of the risk (*20*). There are numerous factors that make it difficult, if not impossible, to estimate the attributable risks associated with hazardous wastes on a national level, including the wide variety of chemicals present in hazardous waste sites, the difficulties in assessing exposure, the obstacles to establishing links between exposure and cancer even when links are present, the small size of exposed populations, and the uncertainties concerning future risks.

Cancer Risks Associated with Water Treatment

Until this century, concerns about the cleanliness of drinking water focused almost exclusively on the presence or absence of pathogens. Ironically, the chlorine used to reduce the risk of infectious disease may account for a substantial portion of the cancer risk associated with drinking water.

Chlorination of drinking water played a central role in the reduction in the mortality rates associated with waterborne pathogens. Water chlorination was first introduced at the Jersey City Water Works in Boonton, New Jersey. The relative ease of use of water chlorination, together with its potent bactericidal action, lead to the rapid dissemination of this treatment technology throughout the United States. Overshadowed by the clear benefits to public health, the potential health risks associated with water chlorination received little attention. This view is evident in an article heralding the opening of the Boonton waterworks, which appeared on the back page of the *New York Times* (*21*). The brief article claimed that, with this process, "any municipal water supply can be made as pure as mountain spring water. Chlorination destroys all animal and microbial life, leaving no trace of itself afterwards" (*21*).

This statement represented the prevailing wisdom until about 20 years ago when halogenated organic compounds, particularly chloroform, were identified in chlorinated drinking water (*22*). A subsequent survey of water supplies showed that these compounds were common in water supplies throughout the United States and that concentrations were far higher in treated surface water than in treated groundwater (*23*). With these revelations came a shift in the basis of our definition of cleanliness in drinking water. New concerns about cancer risks associated with chemical contamination from chlorination by-products have given rise to 25 epidemiologic studies.

Table 2 summarizes the results of a metaanalysis of the cohort and case–control studies that have been conducted to evaluate the association between consumption of chlorinated drinking water and cancer at various sites (*24*). For each cancer site, the pooled results from available studies show elevations in risk, and the risk estimates achieved statistical significance for bladder and rectal cancer. Further analyses in this study suggested that risks increased with increasing exposure and that improvements in exposure assessment yielded higher estimates of risk. Confounding could conceivably explain the observed pattern of association, but stratification into studies that adjusted or did not adjust for confounders does not support such an assertion. Studies that adjusted for population density, smoking, or occupation, did not demonstrate a difference in relative risk estimates. Although it is still possible that the pattern of associations could represent

Table 2. Results from metaanalysis of chlorination by-products and cancer.

Site	n^a	Relative risk estimate	95% Confidence interval		p
Bladder	7	1.21	1.09	1.34	<0.0001
Brain	2	1.29	0.53	3.14	0.56
Breast	4	1.18	0.90	1.54	0.24
Colon	7	1.11	0.91	1.35	0.32
Colorectal	8	1.15	0.97	1.37	0.10
Esophagus	5	1.11	0.85	1.45	0.43
Kidney	4	1.16	0.89	1.51	0.23
Liver	4	1.15	0.94	1.40	0.16
Lung	5	1.01	0.86	1.18	0.94
Pancreas	6	1.05	0.91	1.22	0.48
Rectum	6	1.38	1.01	1.87	0.04
Stomach	6	1.14	0.94	1.38	0.19

[a]Number of studies evaluating specific cancer site.

some systematic bias in the available studies, no specific bias has emerged to explain the observed results.

In summary, the available studies generally support the notion that by-products of chlorination are associated with increased cancer risks. The precise characterization of these risks is somewhat less clear. The broad category of chlorination by-products includes many different compounds, and the carcinogens among these compounds have not been clearly identified. Trihalomethanes are the most prevalent compounds and, given the evidence suggesting that they are animal carcinogens, have been the focus of research and regulation. The chlorination by-products that have been specifically identified, however, account for only about half of the bound chlorine in finished drinking water. Other compounds present in far smaller quantities may pose substantial cancer risks by virtue of high potency (*25*).

The goal of precise characterization of the cancer risk posed by each of the chlorination by-products will probably prove to be unrealistic. A quantitative dose–response relationship has not been well described for any individual compound, much less the entire complex mixture. The relative contributions of different exposure pathways vary among the by-products and have not been well characterized. Nonetheless, given the large number of people who consume chlorinated surface water, the number of cases of cancer potentially attributable to this exposure is substantial. The numbers derived from the metaanalysis suggest that 5000 (95% CI = 2000–7000) cases of bladder cancer per year and 8000 cases of rectal cancer per year (95% CI = 200–14,000) may be associated with consumption of chlorinated drinking water. Although these figures do not provide a precise estimate of risk, the true risk is probably within an order of magnitude of these values.

Since the publication of the metaanalysis, a number of other studies have been completed. McGeehin et al. (*26*) found an elevated risk for bladder cancer comparable in magnitude to the summary estimate of the metaanalysis. Kuovaslo et al. (*27*) found a similar estimate of risk for bladder cancer but did not find an elevated risk for rectal cancer. Kantor (*28*), on the other hand, found a risk for rectal cancer similar to that in the metaanalysis, but an increase in bladder cancer risk associated with chlorination by-products was only observed among smokers. Including these findings within the metaanalysis does not change its results. Nonetheless, these apparent inconsistencies may reflect important differences in the carcinogenicity of the exposures experienced among the various study populations. The complex mixture of compounds that comprise chlorination by-products, the multiple pathways of exposure to those compounds, and the potential for synergy with diet and other exposures may well explain the apparent inconsistencies that exist among the studies included in the metaanalysis.

To stop chlorination of drinking-water to eliminate the elevated cancer risks from chlorination by-products would be foolhardy. Nonetheless, the data provide strong evidence to support expanded efforts in research and development of alternatives to chlorination for the disinfection of drinking-water. Chlorination is particularly effective in preventing recontamination during distribution. Alternatives must provide a similar level of protection. The capacity of chemical disinfectants to kill pathogens generally reflects their strong tendency to react with organic chemicals. The production of by-products may, therefore, be inherent to the chemical disinfection of drinking water. For example, ozone produces aldehydes including formaldehyde and bromate if the source waters contain bromine. These compounds pose a cancer risk that is not yet fully quantified (*29*). Before the widespread introduction of any new method of water treatment, the carcinogenicity of by-products should be carefully evaluated.

Of the other compounds routinely added during the course of drinking-water treatment, fluoride has received the greatest scrutiny as a potential carcinogen. The International Agency for Research on Cancer (IARC) Working Group on Cancer Risks from Fluoridated Drinking Water has concluded that available ecologic studies have been consistent in finding no risk but stopped short of suggesting that flouride was not carcinogenic because the studies were all ecologic in design (*30*). One animal study (*31*) and one case–control study (*32*) suggested that fluoridated water could be linked with osteosarcoma, but these findings will require further confirmation to be considered suggestive of causality. It appears that if flouride poses any cancer risk, the attributable risk is relatively small.

Cancer Risks Associated with Drinking-Water Distribution

The chemical components of pipes, joints, and fixtures can contaminate drinking water after treatment. A broad range of materials are used in these systems. Pipes can be made from metals, primarily iron, copper and lead; plastics, such as polyvinyl chloride and polyethylene; and concrete or asbestos/concrete aggregates. These pipes may be plated or lined with a variety of compounds including zinc, coal tar, asphalt, or vinyl. In addition, bacteria and organic matter frequently coat the inside of pipes within the distribution systems (*33*). All of these can be sources of new contamination, or they can combine with chemicals already in the water to alter the health risks posed by drinking water. In 1979, a study of several medium-size water systems demonstrated increases in mutagenicity of drinking water after passage through the distribution system (*34*). This study did not isolate specific contaminants that might be responsible. Perhaps the most extensively studied contaminant associated with drinking water distribution is asbestos, which can leach from asbestos–concrete pipes. The available research suggests that asbestos from this source does not pose significant human cancer risks (*35–37*). A study by Ashengrau et al. (*38*) showed an increase in leukemia in association with trichlorethylene, which had leached from a plastic liner used in concrete pipes. Other than the negative results of the asbestos studies, the available research does not allow for strong conclusions concerning the magnitude of cancer risks relating to contamination from the distribution system. Further research is needed to identify and quantify risks posed by contamination that occurs during drinking-water distribution.

Emerging Concerns and Potential Cancer Risks

Water is among the most basic requirements for human survival, therefore, emerging health threats related to drinking-water contamination demand careful consideration. Although the identification of potential threats to human health requires a certain degree of speculation, protection of public health requires a willingness to occasionally err in the name of caution. Cancer risks may emerge from the micropollutants and microbial contaminants that can enter our drinking-water supply. Less direct effects may also pose risks.

One focus of current concerns about the potential for micropollutants to cause cancer involves those compounds that mimic naturally occurring, biologically active compounds. Biologically active micropollutants or endocrine disrupters appear to have the ability to disturb normal

intercellular communications. For example, evidence from wildlife biologists, toxicologists, endocrinologists, and epidemiologists demonstrate the potential for estrogenic effects of environmental contaminants among humans (*39,40*). Metabolites of DDT are estrogenic *in vivo* and have been associated with the development of breast cancer in epidemiologic studies (*41,42*). Nonyl-phenol, a common chemical surfactant, increases proliferation in breast tumor cell cultures (*43*). The potential risks from drinking-water contaminants acting through these mechanisms have not been evaluated.

Because of the complex mixture of contaminants, examining cancer risks for each individual compound may not give a complete picture of cancer risks associated with drinking water. An alternative approach is to look at the geographic distribution of neoplasms that might be associated with drinking water. These include cancer of the gastrointestinal tract and bladder cancer (i.e., neoplasms of the mucosal epithelium). Figure 1 provides maps showing clustering of the incidence of site-specific neoplasms among the elderly. By ranking the incidence of the neoplasms of the mucosal epithelium and combining those ranks, we can see where this group of neoplasms might be elevated. A map of the clustering of elevated cancer rates is shown in Figure 2. This map indicates a significant elevation of these cancers in the northeastern United States. To draw conclusions about the link between the geographic distribution and drinking water would, of course, be premature, but any effort to explain this pattern should consider drinking-water contamination to be a possible contributing factor.

Microbial contaminants also have carcinogenic potential. For example, *Schistosoma haematobium* is waterborne, although it is not transmitted by drinking-water, and has been linked to cancer of the urinary bladder (44). Tumor promotion by algal toxins has already been suggested in literature (*45*). Bacteria, parasites, and viruses appear sporadically in most water supplies. The possibility that currently unidentified pathogens in drinking water can cause cancer should not be overlooked.

Water pollution may pose cancer risks other than the direct, toxic effects of exposure to contaminated water. Causal links for the effects described below have not been clearly established, but they are plausible and should be considered in evaluating cancer risks from drinking water.

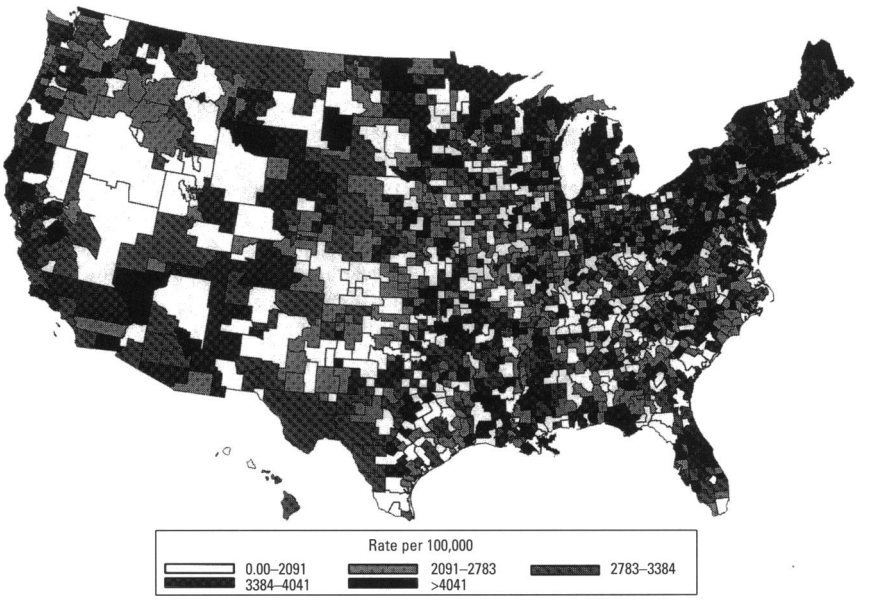

Figure 1. Rank sum map of incidence rates among persons 65 and older for cancers of the esophagus, stomach, colon, rectum, and bladder from 1988 to 1989 (based on Appendix I).

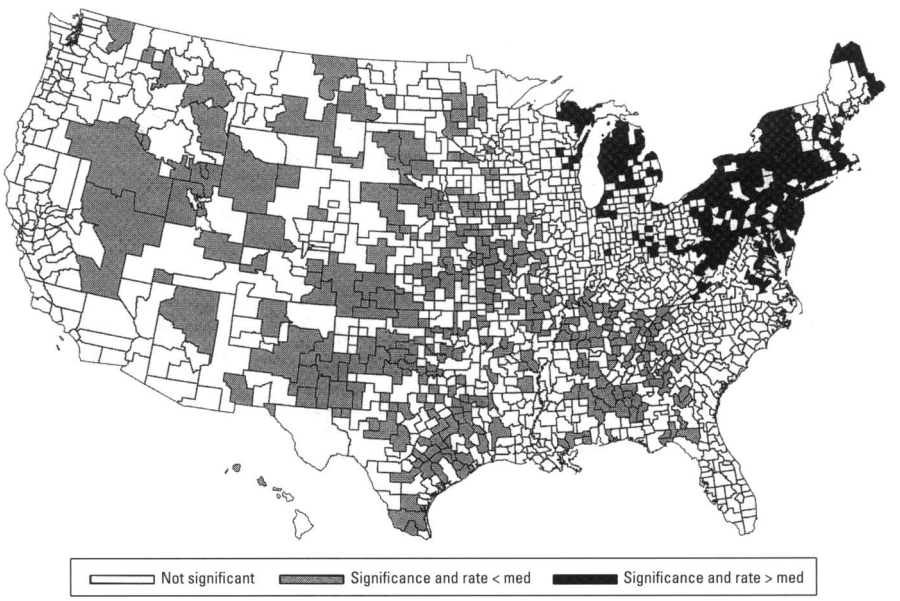

Figure 2. Areas of significant clustering of elevated rates of mucosal neoplasms. Significance of Moran's I: $p<0.0001$.

Contamination of fishing grounds may pose both direct and indirect cancer risks. Persistent, potentially carcinogenic compounds, such as polychlorinated biphenyls, accumulate in the fatty tissues of fish (*46*). Fish consumption is a major exposure pathway for these compounds. In addition, contamination or destruction of spawning grounds may combine with over-fishing to deplete natural fisheries. A dietary shift from fish to red meat, either because of diminished fish stocks or fear of contaminants, could also increase diet-associated cancer risks.

Under conditions of average temperature, humidity, and activity, the human body loses and, therefore, must replace about 2.3 liters of water each day. Two-thirds of

this consumption is in the form of water or some other beverage. Concerns about the health risks or taste of drinking water may induce those who consume tap water to shift to bottled water, or other beverages. These beverages may include sweetened soft drinks and alcoholic beverages, which can pose health risks greater than those associated with drinking water. In addition, the production and disposal of containers for alternative beverages, including bottled water, may lead to the release of carcinogens.

Summary and Prevention Strategies

The cancer risks associated with the major contaminants of drinking water are listed in Table 3. The weight of the evidence suggests that chlorination by-products pose substantial cancer risks that should be reduced. A growing body of evidence supports the possibility that arsenic in drinking water may also carry unacceptable cancer risks. The cancer risks from radon and asbestos in drinking water are less substantial but may require remediation where local conditions dictate. The available evidence does not support assertions of cancer risks associated with fluoridation of drinking water.

For most other compounds present in drinking water, the attributable cancer risks are not clear. Hazardous waste and pesticides may contaminate waters locally and regionally, but the attributable cancer risk is difficult to quantify. Nitrates are more widespread contaminants and more closely linked to human cancer, but evidence is incomplete. Contamination during drinking-water distribution may pose cancer risks, but the epidemiologic evidence is extremely limited. Less conventional cancer risk factors, such as biologically active micro pollutants and pathogens, only present the possibility of risk at present but may emerge as important carcinogens in the future.

Cancer-prevention strategies must focus on source-water purity. In particular, strong source-water protection efforts provide a barrier to emerging cancer risks that have not been identified or fully characterized. Furthermore, failure to protect source water purity will necessitate more extensive water treatment and, in most cases, heavier chlorination. Drinking-water treatment technologies should be evaluated with extreme care and should be reevaluated on a regular basis. The concept of continuous quality improvement should be fully integrated into drinking-water treatment and should include ongoing efforts to develop, evaluate, and implement new treatment technologies. More cost-effective methods for monitoring drinking-water quality need to be aggressively developed. Finally, drinking-water research should be a priority. The consequences of a lack of vigilance with respect to emerging threats in drinking water were felt with devastating impact in Milwaukee, Wisconsin, in 1993, when 400,000 people fell ill during a waterborne outbreak of cryptosporidiosis (*47*). We should view this as a warning and an opportunity for timely intervention to minimize health risks from drinking water.

Table 3. Carcinogenic risk associated with major contaminants of drinking water.

Attributable risk	Contaminant	Point of Entry
Substantial	Chlorination by-products	Treatment
	Arsenic	Source water
Small to moderate	Asbestos	Source water, distribution
	Radionuclides	Source water
Little or none	Fluoride	Treatment
Unknown	Hazardous waste	Source water
	Pesticides	Source water
	Tetrachloroethylene	Distribution
	Nitrates	Source water
	Pathogens	Source water, distribution
	Biologically active micropollutants	Source water, distribution (?)

Appendix I

The map of cancer incidence rates for mucosal cancer was based on the application of the method described below.

Assessing Cancer Incidence Rates

The incidence of cancer of the esophagus, stomach, colon, and urinary bladder for persons over 64 years of age for the period 1988 through 1989 was estimated using Medicare hospital admissions data. The method used to estimate cancer incidence with this database is reported elsewhere (*1–3*). Briefly stated, all patients with a hospital admission for cancer were identified. Patients with no admissions for the site specific cancer diagnosis in the previous 4 years were considered to represent incident cases. From these, age and sex adjusted, race-specific cancer rates were determined.

Localizing Disease Clusters

A disease cluster can be defined as a group of geographic areas that are close to one another with disease rates that are similarly increased or decreased relative to surrounding areas. This can be expressed quantitatively for each analytic area i, as the weighted covariance of its disease rate (x_i) with the rates for the rest of the analytic areas in the study region (x_j) as given by

$$\frac{\sum_j w_{ij}(x_i-\bar{x})(x_j-\bar{x})}{n-1} \qquad [1]$$

where the weights (w_{ij}) are the inverse of the distance between population centroids of the analytic areas (*4*).

If the sizes of the study areas are not homogeneous across the study regions, the weights corresponding to two adjacent areas will vary according to the size of those areas. After modification to accommodate variations in region size, the regional spatial autocorrelation coefficient (RSAC) for analytic area i, R_i, becomes

$$R_i = (x_i-\bar{x})\frac{\sum_j (x_j-\bar{x})(w_{ij}-\bar{w}_i)}{\sqrt{\sum_j (x_j-\bar{x})^2 \sum (w_{ij}-\bar{w}_i)^2}} \qquad [2]$$

The mean and standard deviation of the distribution of RSAC can be reasonably approximated by a normal distribution with an expectation of zero and a standard deviation of $\sigma/(n-2)^{1/2}$ where σ is the standard deviation of x_i and n is the number of analytic areas.

The RSAC was calculated for each analytic area, and the theoretical mean and standard deviation were used to test for significance. Analytic areas that have significantly high RSACs were further classified into two groups based on whether their disease rates were greater or less than the median rate. Analytic areas with significant RSACs and disease rates greater than the median were defined as analytic areas with clustering of elevated disease rates or high clusters. These analytic areas were shaded black in the map. Analytic areas with significant RSACs and disease rates less than the median were defined as analytic areas with clustering of low disease rates or low clusters. When the value of the RSAC was not significant, analytic areas were not shaded and

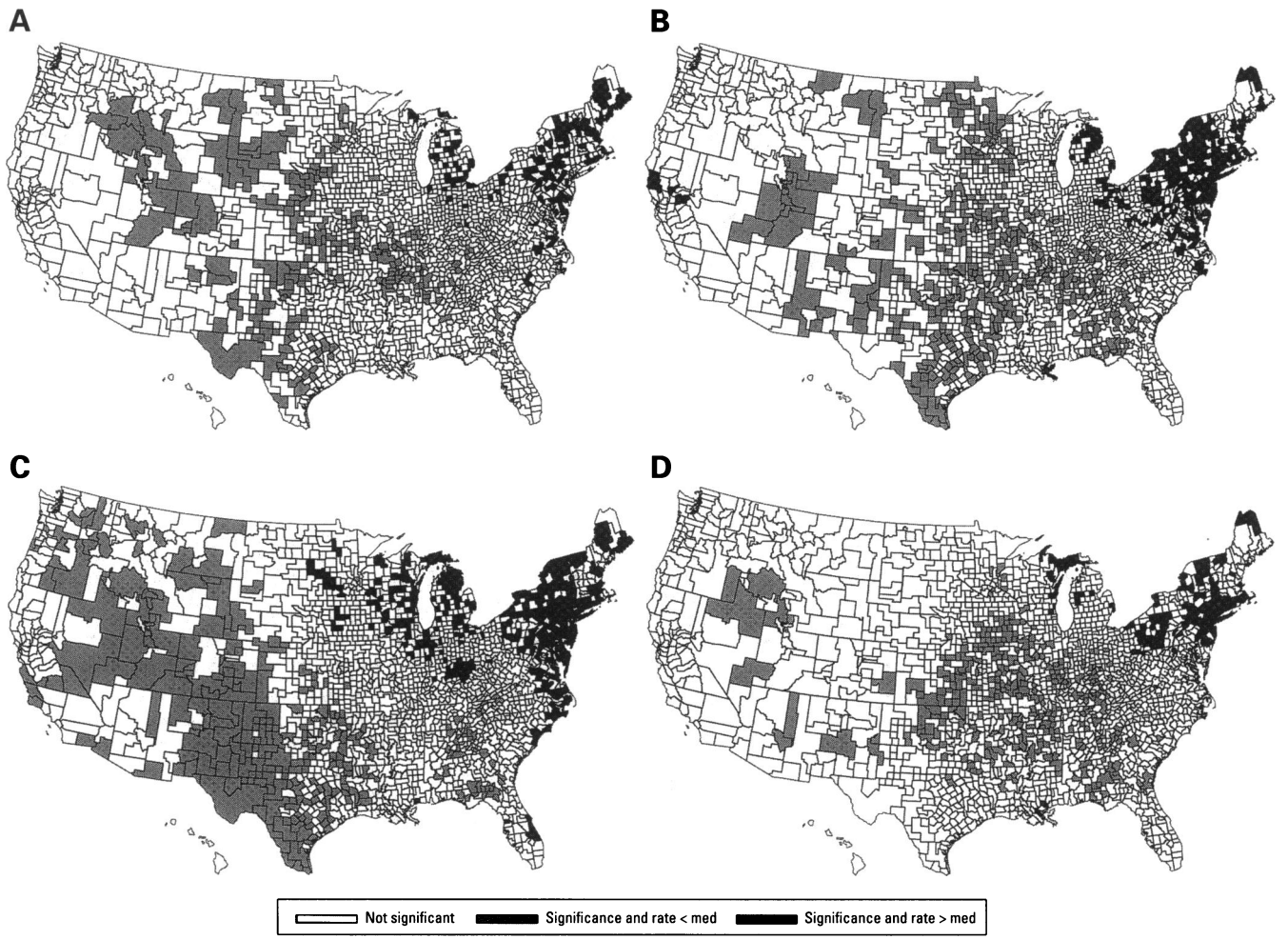

Figure A1. Regional spatial autocorrelation coefficient (RSAC) maps showing localized areas containing statistically significant disease clusters. (*A*) Malignant neoplasm of the esophagus. (*B*) Malignant neoplasm of the bladder. (*C*) Malignant neoplasm of the colon. (*D*) Malignant neoplasm of the stomach. Significance of Moran's I: $p<0.0001$.

represented random spatial structures. Maps depicting the results of these analyses (RSAC maps) were created to evaluate the use of this method as a visual aid to localize areas that contain disease clusters. These methods are described in detail elsewhere (*1,4*). The resulting maps are shown in Figure A1.

Appendix References

1. Morris RD, Munasinghe RL. Aggregation of existing geographic regions to diminish spurious variability of disease rates. Stat in Med 12:1915–1929 (1993).
2. McBean AM, Babish JD, Warren JL. Determination of lung cancer incidence in the elderly using Medicare claims data. Am J Epidemiol 137(2):226–234 (1993).
3. Whittle J, Steinberg EP. Accuracy of Medicare claims data for estimation of cancer incidence and resection rates among elderly Americans. Med Care 29(12):1226-1236 (1991).
4. Munasinghe RL, Morris RD. Localization of disease clusters using regional measures of spatial autocorrelation. Stat Med (in press).

REFERENCES

1. Chen CJ, Kuo TL, Wu MM. Arsenic and cancers (letter). Lancet:1(8582)414–415 (1988).
2. Wu MM, Kuo TL, Hwang YH, Chen CJ. Dose-response relation between arsenic well water and mortality from cancer. Am J Epidemiol 130:1123–1132 (1989).
3. IARC. IARC Monographs on Evaluation of Carcinogenic Risks of Chemicals to Humans; Overall Evaluation of Carcinogenicity: an Updating of IARC Monographs, Vols 1–42, Suppl 7. Lyon:International Agency for Research on Cancer, 1987.
4. Smith AH, Hopenhayn-Rich C, Bates MN, Goeden HM, Hertz-Picciotto I, Duggan HM, Woed R, Kosnett M, Smith MT. Cancer risks from arsenic in drinking water. Environ Health Perspect 97:259–267 (1992).
5. Kanarek MS, Conforti PM, Jackson LA, Cooper RC, Murchio JC. Asbestos in drinking water and cancer incidence in the San Francisco Bay area. Am J Epidemiol 112:54–72 (1980).
6. Polissar L, Severson RK, Boatman ES. A case-control study of asbestos drinking water and cancer risk. Am J Epidemiol 119:456–471 (1984).
7. U.S. Department of Health and Human Services Working

Group. Report on cancer risks associated with the ingestion of asbestos. Environ Health Perspect 72:253–265 (1987).
8. Neuberger JS. Residential radon exposure and lung cancer: an overview of published studies. Cancer Detect Prev 15:435–443 (1991).
9. Crawford-Brown DJ, Cothern CR. A Bayesian analysis or scientific judgment of uncertainties in estimating risk due to 222Rn in U.S. public drinking-water supplies. Health Phys 53:11–21 (1987).
10. Tao XG, Zhu HG. Yu SZ, Zhao ZY, Wang JR, Wu GD, You XF, Li C, Zhi WL, Bao JP, Sun ZQ. Effects of drinking water from the lower reaches of the Huangpu River on the risk of male stomach and liver cancer death. Public Health Rev 19:229–236 (1991-1992).
11. Xu G, Song P, Reed PI. The relationship between gastric mucosal changes and nitrate intake via drinking water in a high-risk population for gastric cancer in Moping County, China. Eur J Cancer Prev 1:437–443 (1992).
12. Tao XG, Zhu HG, Yu SZ, Zhao QY, Wang JR, Wu GD, You XF, Li C, Zhi WL, Bao JP, Sun ZQ. Pilot study on the relationship between male stomach and liver cancer death and the mutagenicity of drinking water in the Huangpu River area. Public Health Rev 19:219–227 (1991-1992).
13. Mirvish SS, Huang Q, Chen SC, Birt DF, Clark GW, Hinder RA, Amyrk TC, DeMeester TR. Metabolism of carcinogenic nitrosamines in the rat and human esophagus and induction of esophageal adenocarcinoma in rats. Endoscopy 25:627–631 (1993).
14. Mirvish SS, Grandjean AC, Moller H, Fike S, Maynard T, Jones L, Rosinsky S, Nie G. *N*-Nitrosoproline excretion by rural Nebraskans drinking water of varied nitrate content. Cancer Epidemiol Biomarkers Prev 1:455–461 (1992).
15. Leclerc H, Vincent P, Vandevenne P. Nitrates de l'eau de boisson et cancer. Ann Gastroenterol Hepatol 27:326–32 (1991).
16. National Research Council. Environmental Epidemiology. Vol 1: Public Health and Hazardous Wastes. Washington:National Academy Press, 1991.
17. Fagliano JM, Berry M, Bove F, Burke T. Drinking-water contamination and the incidence of leukemia: an ecologic study. Am J Public Health 80:1209–1212 (1990).
18. Griffith J, Duncan RC, Riggan WB, Pellom AC. Cancer mortality in US countries with hazardous waste sites and ground water pollution. Arch Environ Health 44:69–74 (1989).
19. Lagakos SW, Wessen BJ, Zelen M. An analysis of contaminated well water and health effects in Woburn, Massachusetts. J Am Stat Assoc 81:583–596 (1986).
20. MacMahon B. Comment. J Am Stat Assoc 81:597–599 (1986).
21. Anonymous. New water purifier: chlorine used in reservoir that supplies Jersey City. New York Times, 7 December 1908; 16.
22. Rook JJ. Formation of halogforms during chlorination of natural waters. Soc Water Treat Exam 23:234–243 (1974).
23. Symons JM, Bellar TA, Carswell JK, DeMarco J, Kropp KL, Robeck GG, Seeger DR, Slocum CJ, Smith BL, Stevens AA. National organics reconnaissance survey for halogenated organics. Am Water Works Assoc 67:634–646 (1975).
24. Morris RD, Audet AM, Angelillo IF, Chalmers TC, Mosteller F. Chlorination, chlorination by-products, and cancer: a meta-analysis. Am J Public Health 82:955–963 (1992).
25. Kronberg L, Holmboom B, Tikkanen L. Identification of the strong mutagen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone and its geometric isomer E-2-chloro-3-(dichloromethyl)-4-oxy-butenoic acid in mutagenic fractions of chlorine-treated humic water and in drinking water. In: Water Chlorination Chemistry, Environmental Impact and Health Effects (Jolley RL, ed). Chelsea, MI:Lewis Publishers, 1987;153–159.
26. McGeehin MA, Reif JS, Becher JC, Mangione EJ. Case–control study of bladder cancer and water disinfection methods in Colorado. Am J Epidemiol 138:492–501 (1993).
27. Koivausalo M, Jaakkola JJ, Varitiainen T, Jakulinen T, Karjalainen S, Pukkala E, Tuomisto J. Drinking-water mutagenicity and gastrointestinal and urinary tract cancers: an ecological study in Finland. Am J Public Health 84:1223–1228 (1994).
28. Kantor KP, Lynch CF, Hildesheim M. Chlorinated drinking water and risk of bladder, colon, and rectal cancers: a case–control study in Iowa, USA. Epidemiology 6:S30 (1995).
29. Bull RJ, Kopfler KC. Health Effects of Disinfectants and Disinfectant By-products. Denver:American Water Works Association, 1992.
30. IARC. Inorganic fluorides used in drinking water and dental preparations. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 27: Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking Water and Dental Preparations. Lyon:International Agency for Research on Cancer, 1982.
31. Bucher JR, Hejtmancik MR, Toft JD, Persing RL, Eustis SL, Haseman JK. Results and conclusions of the National Toxicology Program's rodent carcinogenicity studies with sodium fluoride. Int J Cancer 48:733–737 (1991).
32. Cohn, P. Osteosarcoma and Chlorinated Drinking Water. Trenton, NJ:New Jersey Department of Health, 1993.
33. National Academy of Science. Biological quality of water in the distribution system. In: Drinking Water and Health. Vol 4. Washington:National Academy Press, 1982.
34. Schwartz DJ, Saxena J, Kopfler FC. Water distribution system, a new source of mutagens in drinking waters. Environ Sci Technol 13:1138–1141 (1979).
35. Harrington JM, Craun GF, Meigs JW, Landrigan PJ, Flannery JT, Woodhull RS. An investigation of the use of asbestos cement pipe for public water supply and the incidence of gastrointestinal cancer in Connecticut, 1935-1973. Am J Epidemiol 107:96–103 (1978).
36. Howe HL, Wolfgang PE, Burnett WS, Nasca PC, Youngblood L. Cancer incidence following exposure to drinking water with asbestos leachate. Public Health Rep 104:251–256 (1989).
37. Sadler TD, Rom WN, Lyon JL, Mason JO. The use of asbestos-cement pipe for public water supply and the incidence of cancer in selected communities in Utah. J Commun Health 9:285–293 (1984).
38. Aschengrau A, Ozonoff D, Paulu C, Coogan P, Vezina R, Heeren T, Zhang Y. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. Arch Environ Health 48:284–297 (1993).
39. Colborn T, Vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 101:378–384 (1993).
40. Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel G, Anton-Culver H. Medical hypothesis: xenoestrogens as preventable causes of breast cancer. Environ Health Perspect 101:372–377 (1993).
41. Falck F Jr, Ricci A Jr, Wolff MS, Godbold J, Deckers P. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Environ Health 47:143–146 (1992).
42. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 85:648–652 (1993).
43. Soto AM, Justicia H, Wray JW, Sonnenschein C. *p*-Nonylphenol: an estrogenic xenobiotic released from "modified" polystyrene. Environ Health Perspect 92:167–173 (1991).
44. Gelfand M, Weinberg RW, Castle WM. Relation between carcinoma of the bladder and infestation with *Schistosoma haematobium*. Lancet 502:1249–1251 (1967).
45. Falconer IR, Buckley TH. Tumor promotion by *Microcystis* sp., a blue-green alga occurring in water supplies [letter]. Med J Aust 150:351 (1989).
46. U.S. EPA. National Study of Chemical Residues in Fish. EPA/823-R-92-008b. Washington:US Environmental Protection Agency, 1992.
47. Mackenzie WR, Hoxie NJ, Proctor ME, Gradus MS, Blair KA, Peterson DE, Kazmierczak JJ, Addiss DG, Fox KR, Rose JB, Davis JP. A massive outbreak in Milwaukee of *Cryptosporidium* infection transmitted through the public water supply. N Engl J Med 331:161–167 (1994).